REMARKS

Upon entry of this preliminary amendment, claims 15, 23-26 and 29-39 will be pending in this application, with claims 32-39 withdrawn. Claims 15, 23-26 and 29-31 are presently under examination. Claim 24 has been amended such that it is directed to a method of preparing a vaccine against *Babesia divergens*. Support for inclusion of the term "against *Babesia divergens*" can be found, for example, in Example 3 of Applicants' specification (pp. 26-28). Example 3 describes the evaluation of the ability of one of Applicants' vaccines to guard *against Babesia divergens* in a challenge study using *Babesia divergens*. Claims 25 and 26 have been amended to positively recite certain limitations as method steps. Support for the amendments to these claims can be found, for example, in Applicants' specification page 16, line 23 to page 17, line 7; and from page 18, line 31 to page 19, line 5. Applicants respectfully assert that these claim amendments do not include new matter, and their entry is respectfully requested.

Specification Amendments

The paragraph at page 15, lines 12-20 has been amended to explicitly include the BD-37 core sequence consisting of Serine-25 up to and including Serine-316 from NCBI acc. nr.: CAD19563. Although the examiner is in principle correct that NCBI entries can be modified, Applicants note that the various historic versions are kept, and the different versions are available to the public. Attached as Exhibit A is a printout from the NCBI's website showing a Revision History for CAD19563. This printout shows that accession no. CAD19563 was first seen on February 21, 2002. Clicking on the corresponding date in the table links the browser to the original accession, which is also included as part of Exhibit A. Hence, it is always possible for the public to see a specific version of an accession number, including the original submission.

A close inspection of the priority dates of the captioned application and of the dates listed in the Revision History of Exhibit A reveal that Applicants' specification refers to the February 21, 2002 (i.e., original) accession entry. Applicants point out that this entry was submitted prior to the filing of the captioned application. The amino acid sequence provided in the above amended paragraph (and now also included in the sequence listing) was electronically copied from the first

version of accession no. CAD19563 at the NCBI's website and edited down to include only Serine-25 through Serine-316. Such a peptide should be 292 amino acids long. A character count of this sequence indeed shows only 292 characters were included. See Exhibit B and accompanying sequence listing.

Hence, the paragraph at page 15, lines 12-20 of Applicants' specification has been amended to recite every amino acid of a sequence which had already been fully described at the time of Applicants' filing using other terminology (namely, "Ser-25 up to and including Ser-316 from NCBI acc. nr: CAD19563.") Because this sequence had already been adequately described to a person of ordinary skill in the art in Applicants' specification at the time of its filing, inclusion by way of the present amendment of each amino acid of that same sequence does not constitute new matter.

It is noted that by way of a concurrent filing, Applicants are amending the sequence listing to include SEQ ID NO.:20.

Applicants respectfully assert that these amendments do not include new matter, and their entry is respectfully requested.

Written Description Rejection of Claims 24-26 Under 35 U.S.C. § 112, 1st Paragraph

The Examiner has rejected claims 24-26 under 35 U.S.C. § 112, 1st paragraph for allegedly failing to comply with the written description requirement. Office Action, pages 4-8. Solely to expedite prosecution and not in acquiescence to the rejection, Applicants' have amended claim 24. Accordingly, Applicants request that the Examiner reconsider and withdraw this rejection.

Distinctness Rejection of Claims 24-26 Under 35 U.S.C. § 112, 2nd Paragraph

The Examiner has made various rejections of claims 24-26 under 35 U.S.C. §112, 2nd paragraph for allegedly being vague and indefinite. Office Action, page 8. Claims 24-26 have been amended, and Applicants believe that the rejections are now moot. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejections.

Enablement Rejection of Claims 24-26 Under 35 U.S.C. § 112, 1st Paragraph

The Examiner has rejected claims 24-26 under 35 U.S.C. § 112, 1st paragraph for allegedly failing to comply with the enablement requirement. Office Action, pages 8-10. However, the Examiner does indicate that the specification would enable claims directed to "methods of preparing a vaccine against *Babesia divergens*, comprising mixing a immunogenic composition comprising a saponin adjuvant and a fusion protein comprising a *Babesia* Bd37 polypeptide and a decay accelerating factor peptide with a saponin and a pharmaceutically acceptable carrier." *Id.* at 8. Solely to expedite prosecution and not in acquiescence to the rejection, Applicants' have amended claim 24 such that claims 24-26 are now drawn to the subject matter that the Examiner has identified would be enabled by the specification. Accordingly, Applicants request that the Examiner reconsider and withdraw this rejection.

Rejections of Claims 29 and 31 Under 35 U.S.C. § 112, First and Second Paragraphs

The Examiner rejected claims 29 and 31 under 35 U.S.C. § 112, first and second paragraphs for allegedly not being enabled and for allegedly being indefinite. Office Action, page 11. Applicants have amended their specification to include SEQ ID NO. 20, which was previously described by Applicants as Ser-25 up to and including Ser-316 from NCBI acc. nr: CAD19563. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejections.

Rejections Under 35 U.S.C. §103

Claims 15, 23-26 and 29-31 are rejected under 35 U.S.C. §103 for allegedly being unpatentable over Caras in view of Carcy *et al.* and Gupta *et al.* Office Action, pages 11-13. Applicants respectfully traverse the rejection.

The present application explains at length the difficulty of adjuvanting vaccines with saponins. See page 1, line 8 to page 3, line 14. It is against this technical backdrop that Applicants have presented their invention:

> It is an object of the current invention to provide for the first time an immunogenic composition of a protein antigen adjuvated with a saponin, which does provide an effective immune stimulation without significant adverse local

> effects, at cost effective production levels.
>
> Surprisingly it was found now, that by fusing a hydrophobic peptide to the core of an immunogenic protein, this fusion protein could be combined with free saponin in such a low concentration that the resulting composition does not cause adverse local reactions, while still inducing an efficient immune response.
>
> This is contrary to the common habit of incorporating saponin into ISCOMs or ISCOM-matrix particles for overcoming cytotoxicity. Also this counteracts the customary removal of hydrophobic amino acid (aa) stretches from subunit proteins expressed in a heterologous expression system. The possible loss in yield of fusion protein from the expression system is counterbalanced by the increased immunogenicity in the context of free saponin, and the reduction of adverse local reactions.
>
> Consequently the current invention provides for the first time, a subunit vaccine adjuvated with saponin that is sufficiently safe, immunologically effective and has economic feasibility.

See page 3, lines 17-34.

Caras does not mention or suggest saponin use let alone the optimization of its concentration. Carcy uses the intact full length Bd37 protein in Quil A, but does not describe or suggest at reducing Quil A concentration, shortening Bd37 and attaching a hydrophobic peptide. Gupta merely provides a general description of the use of saponins. None of these publications comes up with the idea of fusing a core protein with a hydrophobic peptide, in order to be able to reduce saponin concentrations to reduce local and toxic reaction, while maintaining a high enough immunogenicity level. Indeed there is no connection between these that would hint a skilled person to solve the problem of Saponin toxicity versus reduced immunogenicity upon lowering the saponin concentration, by attaching a specific fusion peptide to a core protein.

Moreover, the Examiner has engaged in improper hindsight reasoning in combining these references. Nothing in Caras would lead the skilled artisan to select specifically the claimed B. divergens peptide. Indeed, the Examiner states that "Caras discloses a fusion protein comprising decay accelerating factor and *any chose antigen*." Office Action, page 12. This is certainly not enough of a disclosure to lead the skilled artisan to select a B. divergens peptide from the myriad of known peptides that might serve as antigens.

Nothing in the references applied by the Examiner teach or suggest the claimed invention. Accordingly, Applicants request that the Examiner reconsider and withdraw this rejection.

Conclusion

Applicants do not believe that any other fee is due in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **02-2334**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **02-2334**.

Applicants submit that this application is in condition for allowance, and request that it be allowed. The Examiner is requested to call the Undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,

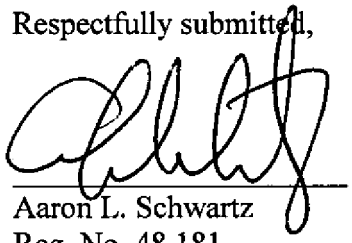

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EXHIBIT A

NCBI

Sequence Revision History

Entrez

Search for Genes
Entrez Gene provides gene-specific data for multiple taxa

Help|FAQ

Batch Entrez: Upload a file of GI or accession numbers to retrieve protein or nucleotide sequences

Check sequence revision history

How to create WWW links to Entrez

LinkOut

My NCBI (Cubby)

Related resources

BLAST

Reference sequence project

Entrez Gene

Clusters of orthologous groups

Revision history for CAD19563

GI	Version	Update Date	Status	I	II
18857691	1	Oct 18 2006 9:06 AM	Live	◉	○
18857691	1	May 5 2004 11:03 PM	Dead	○	◉
18857691	1	Aug 5 2003 2:43 AM	Dead	○	○
18857691	1	Feb 21 2002 11:25 PM	Dead	○	○

Accession CAD19563 was first seen at NCBI on Feb 21 2002 11:25 PM

Protein reviews on the web

1: CAD19563. Reports glycosylphosphati...[gi:18857691] BLink, Links

Features Sequence

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LOCUS       CAD19563                341 aa            linear   INV 18-FEB-2002
DEFINITION  glycosylphosphatidylinositol-anchored merozoite surface protein
            [Babesia divergens].
ACCESSION   CAD19563
VERSION     CAD19563.1  GI:18857691
DBSOURCE    embl locus BDI422214, accession AJ422214.1
KEYWORDS    .
SOURCE      Babesia divergens
  ORGANISM  Babesia divergens
            Eukaryota; Alveolata; Apicomplexa; Piroplasmida; Babesiidae;
            Babesia.
REFERENCE   1
  AUTHORS   Delbecq,S., Precigout,E., Vallet,A., Schetters,T. and Gorenflot,A.
  TITLE     Babesia divergens : cloning and characterization of Bd37, a
            potential vaccine against babesiosis
  JOURNAL   Unpublished
REFERENCE   2  (residues 1 to 341)
  AUTHORS   Delbecq,S.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-DEC-2001) Delbecq S., Laboratoire de Biologie
            Cellulaire et Mo, Faculte de Pharmacie, 15, av. C. Flahault B.P.
            14491, 34093 Montpellier Cedex 5, FRANCE
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                     /db_xref="taxon:32595"
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                     surface protein"
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     CDS             1..341
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ORIGIN
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      121 vvdtdlllkv dstkvdeagk kvkaylekig irgdsveaal dnlmikvyei tkgtvessaq
      181 gtdseelktl llkfsedlka eqelhseakg geallssmkt qhdellkkfa altptfltse
      241 disgyltvpe ygapmnaakw kkvegmihgk lessevpanl kalvaeliel reqmmdllyg
      301 pighhdcaag sgqgsspkkp sfaavpssls aivfgiivsm f
//
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EXHIBIT B

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